REMARKS

Claims 1 and 3-6 remain in the application.

Claim 1 has been amended to exclude the use of free glutamine in the method, support for which can be found in the exemplified formulas, which contain no free glutamine, as well as in the specification at page 7, last paragraph.

In view of the above-amendment, claim 1 has also been amended to delete the earlier entered phrase "as a sole source of glutamine in the liquid composition." This phrase has been removed since the purpose of that phrase was primarily to exclude the use of free glutamine.

Invention Synopsis

The method of the present invention is based in part upon the discovery that N-acetyl-L-glutamine has utility as an oral glutamine supplement in humans. It has now been found that human intestinal tissue deacetylates N-acetyl-L-glutamine, to thus form glutamine for use in the body. As such, N-acetyl-L-glutamine can now be incorporated into oral nutritionals designed for human consumption to thus provide a source of supplemental glutamine. This is especially useful in liquid formulations where N-acetyl-L-glutamine is more stable than free glutamine. Free glutamine is more commonly used in solid or powder product forms.

Applicant found that orally administered N-acetyl-L-glutamine is a highly effective glutamine source, more so than even glutamine itself when administered orally. Applicants conducted a study to evaluate, among other effects, the potential impact of orally administered N-acetyl-L-glutamine versus glutamine on intestinal damage caused by protein-energy malnutrition in pigs. It was found that the deleterious effects of malnutrition on the antioxidant defense system appeared less marked in the intestine of animals that orally consumed the N-acetyl-L-glutamine supplement than in the animals that orally consumed caseinate or glutamine supplements (see Applicant's Specification at page 40, second paragraph.). It was also found that oral N-acetyl-L-glutamine was significantly more effective than caseinate as well as glutamine (oral) in reducing small intestine immunological changes promoted by malnutrition, especially in total cell number and B and T helper subpopulations (see Applicants' Specification at page 41, fourth paragraph).

The data from the study therefore suggest orally administered N-acetyl-L-glutamine would be a surprisingly effective source of nutritional glutamine, more so than even free glutamine itself when administered orally to individuals in need thereof.

Double Patenting Rejection

Claims 1 and 3-6 have been rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-6 of copending and commonly owned Application No. 10/266,317. Responsive to this rejection, submitted herewith is a Terminal Disclaimer under 37 CFR 1.321(b) that specifies that the term of any patent issuing from this application shall not extend beyond the term of any patents issuing from the referenced copending application. Applicants now respectfully request withdrawal of this rejection.

Rejection under 35 USC 102

Claims 1, 3, and 4 have been rejected under 35 USC 102(b) as being anticipated by EP 540 462 (Brouns et al.). Applicant traverses this rejection as it would apply to the amended claims.

Brouns et al. disclose oral compositions comprising L-glutamine (L-glutamine in free amino acid form) or a source thereof (abstract). Such sources may include N-acetyl-L-glutamine (page 2, lines 42-44). The oral compositions may include solid and liquid product forms (page 2, lines 55-57). Since free glutamine is unstable in liquids, the compound in a liquid may be employed in a peptide or N-acetylated form (page 3, lines 57 and 58).

Applicant acknowledges that Brouns et al. may suggest the use of either a peptide form of glutamine, or an N-acetylated form of glutamine, in a liquid, since free glutamine would be unstable in a liquid (page 3, lines 57 and 58). However, Brouns et al. fails to disclose any composition, nutritional or otherwise, that actually contains N-acetyl-L-glutamine.

Instead, Brouns et al. specifically discloses 1) a liquid composition comprising carbohydrates, fat, electrolytes, vitamins, and L-alanyl-L-glutamine (page 4, Example, lines 10-25), 2) a liquid composition comprising L-glutamine, skimmed yogurt, and low carbohydrate raspberry syrup (page 4, lines 30-44), and 3), a liquid composition comprising carbohydrate, electrolyte and L-alanyl-L-glutamine (page 5, lines 2-6).

Applicant submits, therefore, that Brouns et al., in failing to actually disclose a liquid composition comprising N-acetyl-L-glutamine, and in failing to disclose the administration of such a composition in accordance with the presently claimed method, cannot properly be used to support a rejection under 35 USC 102(b).

Applicant requests withdrawal of this rejection as it would apply to the amended claims.

Rejection under 35 USC 103(a)

1. EP 540462 in view of US 3,178,342.

Claim 5 has been rejected under 35 USC 103(a) as being unpatentable over EP 540462 (Brouns et al.) in view of US 3,178,342 (Buzas). Applicant traverses this rejection as it would apply to the amended claims.

Brouns et al. disclose oral compositions comprising L-glutamine (L-glutamine in free amino acid form) or a source thereof (abstract). Such sources include N-acetyl-L-glutamine (page 2, lines 42-44). The oral compositions may include solid and liquid product forms (page 2, lines 55-57). Since free glutamine is unstable in liquids, the compound in a liquid may be employed in a peptide or N-acetylated form (page 3, lines 57 and 58). Brouns et al. fail to actually disclose a liquid composition that contains N-acetyl-L-glutamine.

Buzas discloses an acetyl glutamate salt of dimethyl aminoethanol (col. 1, lines 44-54) and is cited by the examiner for its disclosure of salt forms of dimethyl aminoethanol, that the examiner contends can now be reapplied to N-acetyl-L-glutamine to thereby suggest the recited salt forms of N-acetyl-L-glutamine of claim 5.

Applicants acknowledge that Brouns et al. may suggest the use of either a peptide form of glutamine, or an N-acetylated form of glutamine, in a liquid, since free glutamine would be unstable in a liquid (page 3, lines 57 and 58). However, Brouns et al. fails to specifically disclose any composition, nutritional or otherwise, that actually contains N-acetyl-L-glutamine.

Instead, Brouns et al. specifically discloses 1) a liquid composition comprising carbohydrates, fat, electrolytes, vitamins, and L-alanyl-L-glutamine (page 4, Example, lines 10-25), 2) a liquid composition comprising L-glutamine, skimmed yogurt, and low

carbohydrate raspberry syrup (page 4, lines 30-44), and 3), a liquid composition comprising carbohydrate, electrolyte and L-alanyl-L-glutamine (page 5, lines 2-6).

None of the disclosed compositions from either reference actually contain N-acetyl-L-glutamine. Brouns et al. may suggest the use of N-acetyl-L-glutamine, but it doesn't disclose a composition containing it; Buzas is completely silent as to N-acetyl-L-glutamine.

Even if the skilled artisan were motivated by Brouns et al. in view of Buzas to formulate a nutritional liquid comprising N-acetyl-L-glutamine, one would not have expected that the new formulation would result in a composition that is more effective in many respects as a glutamine source than a composition containing free glutamine itself.

To that point, Applicants conducted a study to evaluate the potential effects of N-acetyl-L-glutamine versus free glutamine on intestinal damage caused by protein-energy malnutrition in pigs (page 37, Example 4, lines 20-22). Applicants found that the deleterious effects of malnutrition on the antioxidant defense system appeared less marked in the intestine of animals that consumed the N-acetyl-L-glutamine supplement than in the animals that consumed the caseinate or glutamine supplements (page 42, lines 7-9). Applicants also found that the N-acetyl-L-glutamine-supplemented group performed better than the glutamine or caseinate supplemented groups, showing statistically significant differences, to reduce small intestine immunological changes promoted by malnutrition, especially in total cell number and B and T helper subpopulations (page 43, lines 22-25).

The above study suggests that N-acetyl-L-glutamine has a positive effect on the cells of the small intestine, even beyond that of glutamine. Additionally, electron transmission micrographs of enterocyte cytoplasm from healthy and malnourished pigs shown in Figures 7 and 8 of Applicants' Specification show that N-acetyl-L-glutamine is more effective than glutamine at preventing the overt signs of inflammation in the epithelial lining of the gastrointestinal tract.

The data set forth in the Brouns et al reference showed that compositions containing either free glutamine (L-glutamine) or L-alanyl-L-glutamine increased plasma glutamine concentrations, but neither had an impact on the tested clinical outcome (time to exhaustion during exercise) (page 4, lines 47-51; page 5, lines 11-15). Brouns et al fails to disclose any formulation or testing of compositions comprising N-acetyl-L-glutamine.

Applicant submits that one of ordinary skill in the art would look to the Brouns et al. data and conclude that free glutamine is no more or less effective than other glutamine derivatives. As noted above, however, Applicants found that N-acetyl-L-glutamine was more effective than free glutamine itself in several tested parameters. These unexpected results from an otherwise novel composition and method of using the composition, supports patentability of the claimed method over Brouns et al. in view of Buzas.

In view of the amendments presented and the foregoing remarks, Applicant requests withdrawal of this rejection as it would apply to the amended claims.

2. EP 540462 in view of Klimberg et al.

Claim 6 has been rejected under 35 USC 103(a) as being unpatentable over EP 540462 (Brouns et al.) in view of Klimberg et al., Arch Surg, Vol 125, Aug 1990, 1040-1045 (Klimberg). Applicant traverses this rejection as it would apply to the amended claims.

As described supra, Brouns et al. discloses oral compositions comprising L-glutamine (L-glutamine in free amino acid form) or a source thereof (abstract). Such sources include N-acetyl-L-glutamine (page 2, lines 42-44). The oral compositions may include solid and liquid product forms (page 2, lines 55-57). Since free glutamine is unstable in liquids, the compound in a liquid may be employed in a peptide or N-acetylated form (page 3, lines 57 and 58). Brouns et al. fail to actually disclose a liquid composition that contains N-acetyl-L-glutamine.

Klimberg discloses oral glutamine for use in mice exposed to whole abdominal radiation. Glutamine ingestion diminished bloody diarrhea and the incidence of bowel perforation (abstract). The tested diet comprised an isonitrogenous solution with 1% glucose and 3% glutamine (p. 1040, col 2, last para.; p. 1041, col. 1, lines 1 and 2). Klimberg fails to disclose N-acetyl-L-glutamine.

Applicants acknowledge that Brouns et al. may suggest the use of either a peptide form of glutamine, or an N-acetylated form of glutamine, in a liquid, since free glutamine would be unstable in a liquid (page 3, lines 57 and 58). However, neither Brouns et al. nor Klimberg specifically disclose any composition, nutritional or otherwise, that actually contains N-acetyl-L-glutamine.

Instead, Brouns et al. specifically discloses 1) a liquid composition comprising carbohydrates, fat, electrolytes, vitamins, and L-alanyl-L-glutamine (page 4, Example, lines 10-25), 2) a liquid composition comprising L-glutamine, skimmed yogurt, and low carbohydrate raspberry syrup (page 4, lines 30-44), and 3), a liquid composition comprising carbohydrate, electrolyte and L-alanyl-L-glutamine (page 5, lines 2-6).

None of the disclosed compositions from either reference actually contain N-acetyl-L-glutamine. Brouns et al. may suggest the use of N-acetyl-L-glutamine, but it doesn't actually disclose such use; Klimberg discloses 3% glutamine solutions in rats, but is completely silent as to N-acetyl-L-glutamine.

Even if the skilled artisan were motivated by either reference to formulate a nutritional liquid comprising N-acetyl-L-glutamine, one would not have expected that the new formulation would result in a composition that is more effective in many respects as a glutamine source than a composition containing free glutamine itself.

The discussion of concerning the unexpected benefits from the claimed compositions and methods are described above.

The data set forth in the Brouns et al reference showed that compositions containing either free glutamine (L-glutamine) or L-alanyl-L-glutamine increased plasma glutamine concentrations, but neither had an impact on the tested clinical outcome (time to exhaustion during exercise) (page 4, lines 47-51; page 5, lines 11-15). Brouns et al fails to disclose any formulation or testing of compositions comprising N-acetyl-L-glutamine.

Applicants submit that one of ordinary skill in the art would look to the Brouns et al. data and conclude that free glutamine is no more or less effective than other glutamine derivatives. As noted above, however, Applicants found that N-acetyl-L-glutamine is more effective than free glutamine itself in several tested parameters. These unexpected results from an otherwise novel composition and method, supports patentability of the claimed method over Brouns et al. in view of Klimberg.

The Klimberg reference likewise fails to disclose or suggest Applicant's unexpected results. Klimberg is completely silent as to the use of N-acetyl-L-glutamine, and therefore clearly fails

to make any suggestion whatsoever of Applicant's unexpected finding associated with N-acetyl-L-glutamine use.

In view of the amendments presented and the foregoing remarks, Applicant requests withdrawal of this rejection as it would apply to the amended claims.

Conclusion

Applicant respectfully requests reconsideration of this application and allowance of claims 1 and 3-6.

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